Gut microbiota and metabolic disorders. by E. Munukka[1,2], S. Pekkala[2], P. Wiklund[2], A. Rintala[1], M. Alen[3]. P. Huovinen[1]and S. Cheng[2,4] , [1] *Department of Medical Microbiology and Immunology, University of Turku, Finland Department of Health Sciences, [2] University of Jyväskylä, P.O.Box 35, 40014 University of Jyväskylä, Finland, [3]Department of Medical Rehabilitation, Oulu University Hospital, Oulu, Finland and Institute of Health Sciences, University of Oulu, Finland, [4] Department of Physical Education, Shanghai Jiao Tong University, Shanghai, China*

The prevalence of obesity and metabolic disorders are reaching epidemic proportions all over the world (1,2). Obesity and related chronic comorbidities such as insulin resistance (IR), type II diabetes (T2D), fatty liver diseases, hypertension and cardiovascular disease (CVD) are considered to be the major threats for the general health of human population (1,2). Recent evidence suggests that dysbiotic gut microbiota composition may affect the onset and progression of obesity and metabolic disorders (3-6). For example, gut microbiota regulates and controls the host's metabolic functions, such as *de novo* lipogenesis and triglyceride storage in adipose and hepatic tissue (3,4). Gut-derived bacterial fragments and metabolites might have an important role in the development and progression of fat accumulation, and may contribute to the onset of inflammation and further insulin resistance (IR) (3,4). However despiting the accumulating evidence that highlights the role of gut microbiota in obesity and related metabolic disorders, the underlying mechanisms in humans are still unclear.

The aim of our research project is to elucidate the contribution of gut microbiota composition to obesity-related metabolic disorders such as hepatic fat accumulation, metabolic syndrome and sleep apnea. Specifically, we are interested in the possible Toll-like receptor 5 (TLR5) -mediated metabolic changes in humans. TLR5 is a pattern recognition receptor that responds to bacterial flagellin (7). It has been shown to be overexpressed in the visceral adipose tissue of diet-induced obese and genetically obese *ob/ob* mice (8). However, the exact metabolic consequences of the TLR5's over-expression are not known.

The role of TLR5 in the metabolism will be studied with the flagellin in the cultured human adipocytes and hepatocytes. Further, the potential TLR5 activators, such as flagellated members of gut microbiota are characterized in women having higher expression levels of TLR5 signaling pathway genes in their adipose tissue, thus we aim to identify a possible link to increased fat mass and adipose tissue inflammation.

Recently we reported that dysbiotic gut microbiota composition is associated with high hepatic fat content (HHFC) in humans (9). Middle-aged men and women with high, hepatic fat content (HHFC, n = 10) differed in their gut microbiota composition from those with low hepatic fat content (LHFC, n = 21). In addition, gut microbiota differences associated with body composition, serum biomarkers and abdominal adipose tissue inflammation. In a current study hepatic fat content (HFC) was measured *in-vivo* using proton magnetic resonance spectroscopy (^{1}H MRS) (10). Gut microbiota composition was profiled from fecal samples by 16S rRNA fluorescence *in situ* hybridization and flow cytometry (11). Gene expression in subcutaneous adipose tissue biopsies was analyzed using Affymetrix microarrays and quantitative PCR.

We found that the amount of *Faecalibacterium prausnitzii*, and was lower in HHFC compared to LHFC group ($P < 0.05$), and inversely correlated with hepatic fat content ($P < 0.05$ for all) (Figure 1). In addition, several inflammation-related genes were over-expressed in adipose tissue of the HHFC group, and their expression correlated with HFC. In conclusions, people with elevated hepatic fat significantly differ in their gut microbiota composition compared to their counterparts with low hepatic fat content. We conclude that the adipose tissue inflammation might serve as an important link between the gut microbiota and hepatic fat accumulation.

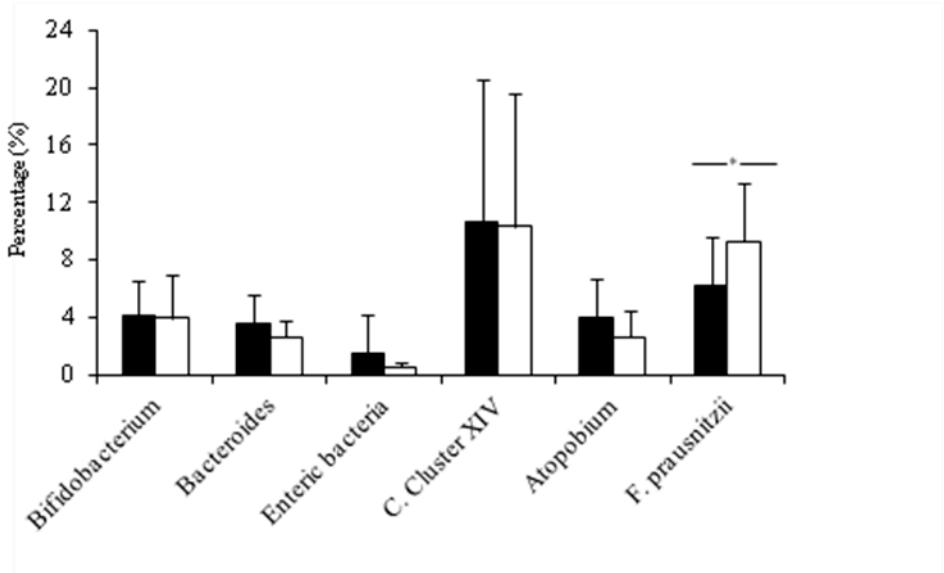

Figure 1. Proportions (%) of bacterial groups. Bars indicate means and segment of lines SD. Differences between the HHFC (black) and LHFC (white) groups were calculated by using

Student's t-test, * $p < 0.05$, ** $p < 0.01$. Proportions (%) of fecal bacterial groups. Bars indicate mean values and segment of lines SD. * $p < 0.05$

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